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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/964,261	09/25/2001	Ilse De Canck	IGJ-002	1026

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,261	CANCK ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,7,10,22,24 and 26-38* is/are pending in the application.

4a) Of the above claim(s) *7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 5, 10, 22, 24, 26-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the amendment filed September 17, 2003. Applicants amendments and arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Election/Restrictions

2. Applicant's election of Group I, claims 1-17 and 22-25 in the response of September 17, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that the claims limited to specific SEQ ID Nos and to specific positions/loci to which the primer hybridizes have been examined only to the extent that they read on the elected invention of primers consisting of SEQ ID NO: 144 and 1 for exon 2; SEQ ID NO: 104 and 147 for exon 3; and SEQ ID NO: 205 and 311 for exon 4 and methods which amplify the target positions of 67, 181 and 501. It is again noted that the requirement to elect specific nucleotide sequences and nucleotide positions is a restriction requirement and not an election of species. Claim 7 is withdrawn from consideration as being drawn to a non-elected invention in that the claim is drawn to a method that requires the use of the non-elected primer pair of SEQ ID NO: 104 and 156. The subject matter of the additional SEQ ID Nos and additional nucleotide positions are also withdrawn from consideration. The restriction requirement is made final.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 5, 10, 22, 24, 26, 27, 28, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 5, 10, 22, 24, 26, 27, 28-33, and 36 are indefinite over the recitation of "wherein said position constitute the 3' end of the primer" because it is not clear as to what this phrase is intended to encompass. It is unclear as to what constitutes such a primer – e.g. whether said primer terminates at the 3' end at a position that has the same nucleotide as the position set forth in the claims, such that only the 3' nucleotide is defined and the remainder of the primer may be of any nucleotide composition. It is unclear as to whether this 3' position is the complement of the nucleotide stated or is identical to the nucleotide stated.

Claims 1, 4, 5, and 22 are indefinite over the recitation of "separately in one reaction." This phrase is not specifically defined in the specification and it is not clear as to what is intended to be encompassed by this phrase. For example, it is not clear as to whether this phrase refers to the fact that different primer pairs are used to amplify each exon independently or if this refers to the fact that the exons are amplified at different

time points. Similarly claims 28-33 and 36 are indefinite over the recitation of "amplifying exon 2, exon 3 and exon 4 of HLA-A alleles separately in one reaction."

Claim 22 is indefinite over the recitation of "The method for typing or subtyping HLA-A alleles comprising the amplification method according to claim 1." Firstly, the phrase "The method" lacks proper antecedent basis since the claim does not previously refer to a method for typing or subtyping. Secondly, it is not clear as to how this claim is intended to be limited from claim 1. Claim 1 recites only a method for amplifying HLA-1. The claim does not include steps of typing or subtyping. Further, claim 22 does not include steps that result in the typing or subtyping of HLA-A alleles. Accordingly, it is not clear as to whether claim 22 is intended to be drawn to the same subject matter as claim 1 or if claim 22 is intended to be limited to methods for typing or subtyping, it is not clear as to how the step of amplifying HLA-A alleles results in the typing or subtyping of HLA-A alleles. Similarly, claim 36 is indefinite over the recitation of "The method for typing or subtyping HLA-A alleles comprising the amplification method according to claim 28."

Claims 35 and 38 are indefinite because the phrases "the reverse primer" and "the forward primer" lack proper antecedent basis.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section

> 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claim 10 and newly added claims 26, 27, 34 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Yang (US Patent No. 6,030,775).

Yang (see, for example, columns 4-6) teaches methods for amplifying HLA-A using locus-specific primers and further analyzing the amplified sequences to determine the type or subtype of the HLA-A allele. In particular, Yang teaches amplifying exon 2 and 3 together in a single reaction using one set of primers or amplifying exon 2 and 3 separately using 2 sets of amplification primers. Yang (column 5) states that "It will be appreciated, however, that exons 2 and 3 could be amplified individually by selecting a second amplification primer for exon 2 and a first primer for exon 3 which hybridize with intron 2 (SEQ ID Nos: 2, 5, and 8) ." The reference (column 5, lines 52-54) also states that "(p)referably, both primers will be locus-specific in their hybridization to the HLA gene." Primers are exemplified which hybridize to intron 1 and intron 2 and which amplify exon 2 and primers which hybridize to intron 2 and intron 3 and amplify exon 3 (see columns 4-6). Yang (column 6, lines 2-7) states that "amplification primers which are a few bases longer by virtue of adding additional complementary bases, amplification primers which are a few bases shorter, and complementary amplification primers may be used in the method of the present invention. Other potential sites for HLA-A locus specific primers are highlighted in FIG. 4." Further, additional locus-

specific primers within introns 1 and 2 are shown in Figures 2 and 3 (see also column 5). Yang (column 17) also discloses kits containing the locus-specific primers and primer pairs which specifically hybridize to intron 1, intron 2, intron 3 of the HLA-A gene. Accordingly, Yang teaches forward and reverse locus-specific primers that hybridize to sequences in intron 2 and intron 3 and hybridize to sequences for the amplification of exon 2 and exon 3.

It is noted that claim 10 has been amended to recite that the primer hybridizes to a locus-specific target sequence in intron 3, wherein the target sequence is situated at position 501 as defined by SEQ ID NO: 444, wherein position 501 constitutes the 3' end of the primer. The claim does not require that the primer consists of any particular sequence of SEQ 444 or that the primer hybridizes under a specific set of conditions to SEQ ID NO: 444. It is further noted that the recitation in the amended claim of "for use in the locus-specific amplification of exon 3 of HLA-A alleles" is only a recitation of the intended use of the product and does not further limit the structure of the claimed primer or the scope of the claim. Accordingly, this claim reads on any primer that hybridizes at the 3' end to position 501. Position 501 of SEQ ID NO: 444 is a G. Thereby the claim appears to include any primer that has a C at its 3' terminus. Yang exemplifies a number of primers that terminate in a C, such as the primer set forth at column 5, line 63, designated as SEQ ID NO: 13 in Yang. Further, the nucleotide at position 181 of SEQ ID NO: 315 is a "C." Yang teaches primers which hybridize to intron 2 and terminate with a G, such as the primer in Figure 3 of "GCTGACCKYGGGGTCSG."

Yang also teaches primer mixes with primers that can hybridize to intron 2, and intron 3 of HLA-A.

Response to arguments:

In the response of September 17, 2003, Applicants state that Yang does not teach locus specific primers. However, Yang clearly defines the primers as being locus-specific. Applicants appear to be reading a definition into the phrase "locus-specific" that is distinct from that used by Yang. However, Applicants have not defined locus-specific as having a meaning that is different from that used by Yang and recognized in the art. There is no specific limitation in the claims that distinguish Applicant's locus-specific primers over the locus-specific primers of Yang. Applicants point out that the first primer listed in Figure 2 contains a variable nucleotide, i.e., an "S", such that the sequence terminates in a G or C. Applicants thereby conclude that "the primers exemplified by Yang are not locus specific." However, the fact that the primer is identical to more than one nucleotide sequence does not mean that the primer is not locus-specific. Again, Applicants are reading limitations into the claims. The claims do not require a primer that is identical or 100% complementary to one single nucleotide sequence. Further, it is improper to draw the conclusion that Yang does not teach locus specific primers because one out of the multitude of primers that Yang teaches includes a variable nucleotide position. Such a conclusion does not take into consideration the full teachings of Yang. Figure 2 of Yang is not intended to exemplify only locus-specific primers. As stated by Yang (column 4), "FIGS. 2, 3 and 4 shows combined sequences (Seq. ID Nos. 1-9) for introns 1, 2 and 3 respectively, together with suitable locations for

binding amplification primers. These sequences are consensus sequences derived from the individual aligned sequences determined for each intron as shown in FIGS. 5A-5H."

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 5, 10, 22, 24, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang in view of Mullis.

Yang (see, for example, columns 4-6) teaches methods for amplifying HLA-A using locus-specific primers and further analyzing the amplified sequences to determine the type or subtype of the HLA-A allele. In particular, Yang teaches amplifying exon 2 and 3 together in a single reaction using one set of primers or amplifying exon 2 and 3 separately using 2 sets of amplification primers. Yang (column 5) states that "It will be appreciated, however, that exons 2 and 3 could be amplified individually by selecting a second amplification primer for exon 2 and a first primer for exon 3 which hybridize with intron 2 (SEQ ID Nos: 2, 5, and 8) ." The reference (column 5, lines 52-54) also states that "(p)referably, both primers will be locus-specific in their hybridization to the HLA

gene." Primers are exemplified which hybridize to intron 1 and intron 2 and which amplify exon 2 and primers which hybridize to intron 2 and intron 3 and amplify exon 3 (see columns 4-6). Yang (column 6, lines 2-7) states that "amplification primers which are a few bases longer by virtue of adding additional complementary bases, amplification primers which are a few bases shorter, and complementary amplification primers may be used in the method of the present invention. Other potential sites for HLA-A locus specific primers are highlighted in FIG. 4." Further, additional locus-specific primers within introns 1 and 2 are shown in Figures 2 and 3 (see also column 5). Yang (column 17) also discloses kits containing the locus-specific primers and primer pairs which specifically hybridize to intron 1, intron 2, intron 3 of the HLA-A gene. Accordingly, Yang teaches a method for amplifying exon 2 using a reverse primer that specifically hybridizes to a locus specific sequence in intron 2 of HLA-A and methods for amplifying exon 3 using a forward primer that specifically hybridizes to a locus specific sequence in intron 2 of HLA-A or a reverse primer which specifically hybridizes to a locus-specific sequence in intron 3 of HLA-A. Yang does not specifically exemplify a method in which exon 2 and exon 3 are separately amplified. However, in view of the specific teaching of Yang of separately amplifying exon 2 and 3 and the teachings of Yang as to locus-specific primers for independently amplifying exon 2 and 3, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have independently amplified exons 2 and 3 in order to have provided an effective means for analyzing the sequences of exons 2 and 3 and for determining an individual's HLA-A haplotype.

Additionally, Mullis (see for example column 10) teaches multiplex amplification methods in which multiple sets of primers are used to simultaneously amplify and detect different target sequences.

Accordingly, in view of the specific teaching of Yang of separately amplifying exon 2 and 3 and the teachings of Yang as to locus-specific primers for independently amplifying exon 2 and 3 and in view of the teachings of Mullis of performing multiplex amplification methods, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have independently amplified exons 2 and 3 in order to have provided an effective, rapid and efficient means for analyzing the sequences of exons 2 and 3 and for characterizing an individual's HLA-A haplotype.

Secondly, Yang does not teach primers which hybridize to a locus-specific target sequence situated at position 67, 181 of HLA-A intron 2 or position 501 of HLA-A intron 3.

However, Yang teaches the sequences of intron 1, 2 and 3 for 13 HLA-A types (see Figure 5) and for several HLA-B and HLA-C types. Yang also teaches a consensus sequence for each of these introns. The alignments provided by Yang identify nucleotide sequences which are conserved and those which are variable. As shown by the alignment of Yang, the sequences at and surrounding positions 67 and 181 of intron 2 and position 501 of intron 3 are conserved amongst the HLA-A types. Further, Yang teaches that locus-specific primers are designed by comparing the sequence alignments set forth in Figures 5A-5H and identifying the conserved sequences (see column 4). Yang also states (column 6) that "(a)s is the case of the first amplification primer, amplification primers which are made a few bases longer by virtue of adding additional complementary bases, amplification primers which are a few bases shorter, and complementary amplification primers may be used in the method of the present invention. Other potential sites for HLA-A locus specific primers are highlighted in FIG.4." Additionally, at column 9, Yang states that "the amplification primers are designed with the specificity-dependent nucleotide(s) on the terminal 3'-prime end."

In view of the teachings of Yang, including the teachings of the sequence alignment of introns 2, 3 and 4 of HLA-A, HLA-B and HLA-C and the guidance provided by Yang as to how to select additional locus-specific primers, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated additional primers, including the primers of the present invention which terminate at positions 67 and 181 of intron 2 and position 501 of intron 3, because such primers would have hybridized to conserved HLA-A sequences and would have provided an equally effective means for separately amplifying exons 2 and 3 of HLA-A. In the absence of unexpected results, primers which hybridize to sequences identified by Yang as being conserved are considered to be obvious variants of the multitude of primers disclosed by Yang which have the attributes of being locus-specific and useful for individually amplifying exons 2 and 3 of HLA-A. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers in a kit for the convenience of practioners in the art wishing to amplify and characterize exon 2 and 3 sequences.

Response to Arguments:

In the response filed September 17, 2003, Applicants state that "Yang fails to teach or suggest, or provide any guidance or motivation whatsoever, regarding how to select for **locus-specific** primers. The only phrase regarding the selection of the primers mentioned by Yang is in column 4, lines 16-19, where the authors state that that "it will be advantageous to select primers to avoid variable bases, although in some of the primers discussed, intra-locus variation is taken into account." However, Applicants have not accurately characterized the teachings of Yang. Yang does in fact exemplify locus specific primers. See, for example, columns 5-6. Additionally, Yang does provide guidance for selecting additional primers. For example, Yang provides a comparison of

the sequences of intron 1, 2 and 3 for 13 HLA-A types (see Figure 5) and for several HLA-B and HLA-C types. This comparison immediately identifies the nucleotides that are conserved between the HLA-A types and which are different between the HLA-A, B and C types. Yang (column 4) states that "amplification of exons 2 and 3 is preferably performed using at least one locus-specific primer which specifically hybridizes to a portion of intron 1 or intron 3. As used in the specification and claims hereof, the primers which "specifically hybridize" to the introns are primers which permit locus-specific amplification by having a sequence which is exactly complementary to the expected sequence of a portion of the intron so that binding and amplification can occur, but which is not complementary to a region on any of the other HLA Class I genes." At column 5, Yang states that "In addition to primers binding to the non-coding strand, it will be appreciated that complementary primers which bind to the corresponding portions of the coding strand could be used with a compatible second primer." Yang also states that "Amplification primers useful in the present invention are generally from 10 to 40 bases in length, more preferably from 21 to 35 bases in length. Within this size range, we have identified locus-specific, group specific and allele-specific primers for each of the classical HLA Class I genes" (see column 5) At column 9, Yang states that "By keeping the PCR conditions stringency, the primer pairs will not non-specifically amplify other related alleles. The amplification primers are designed with the specificity-dependent nucleotide(s) on the terminal 3'-prime end." Accordingly, Yang does provide the ordinary artisan with sufficient guidance and motivation to obtain additional primers and to particularly obtain the presently claimed primers which terminate at the 3' end at a position unique to the HLA-A locus.

Applicants state that page 4 of the present specification teaches that locus-specific priming sites are scarce and that separate locus-specific amplification of exon

2, 3 and/or 4 is not evident. However, the sequence comparison of Yang specifically identifies the location of nucleotides that are variable between HLA-A, B and C types and specifically teaches that exons 2 and 3 can be amplified independently of one another. Further, it is unclear as to how on one hand applicants can argue the unpredictability and apparent difficulty in developing primers, and yet the claims include primers that are not defined in terms of their sequence but only in terms of the 3' nucleotide. The complete sequence of a primer determines its annealing and amplification properties – these properties are not determined solely on the bases of the nucleotide present at the 3' end. Further, Applicants claims include primers which do not even include the recitation of a defined 3' end. Applicants should explain why on the one hand they have enabled any locus-specific primer for amplifying exon 2, 3 or 4, and yet the prior art which provides the same level of guidance as that provided by applicants has not enabled primers for amplifying these exons.

Applicants again state Yang does not exemplify a single locus-specific primer and again cite one primer taught in Figure 2 and characterize this primer as not being locus-specific because this primer includes a variable nucleotide. As discussed above, Yang does not teach that each primer set forth in Figure 2 is locus specific. Yang does exemplify throughout the patent locus-specific primers – see, for example column 5. Applicants comments regarding the fact that Yang does not exemplify that exon 2 and 3 can be separately amplified have been considered. However, amplification methods in which primers are used to amplify 2 distinct locations in one reaction are well known in the art, as are the criteria for selection of primers for performing such methods. Further, multiplex amplification methods are specifically disclosed by Mullis. Applicants have not provided any evidence as to why co-amplification of exons 2 and 3 would provide an

especially difficult challenge for the ordinary artisan. The fact that amplification is more efficient when shorter regions are amplified is well known in the art.

6. Claims 28-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang in view of Mullis and further in view of Date (Tissue Antigens (1996) 47:93-101) and Schletinga (Human Immunology (1997)57:120-128).

The teachings of Yang and Mullis are presented above. As discussed above, Yang teaches locus-specific primers which hybridize to intron 3 and teaches that the complements of primers may be used for amplification. Yang also provides an alignment of 13 intron 3 sequences from different HLA-A types, and from different HLA-B and HLA-C types and provides extensive guidance for the selection of additional locus-specific primers that hybridize to intron 3. Yang teaches individually amplifying exon 2 and exon 3 of HLA-A, but does not exemplify amplifying exon 4 of HLA-A.

Date teaches amplifying exon 4 using a reverse primer that hybridizes to exon 4 and determining the sequence of the amplified fragments of exon 4 (see pages 94-95 and Figure 1). Date also teaches that sequences within exon 4 can be used to distinguish different HLA-A types from one another (see pages 98-99).

Scheltinga (page 124 and Figure 1) teaches a primer that hybridizes to sequences within intron 4 and the sequencing of exon 4 using primers which hybridize to intron 3 and intron 4. The reference teaches amplification of exon 4 using a reverse primer that hybridizes to exon 5. Scheltinga also teaches that a polymorphism was identified in exon 4 which is useful in distinguishing between HLA-A types.

In view of the teachings of Date and Scheltinga, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modified the method

of Yang so as to have also amplified exon 4 using a forward primer that hybridizes to a locus-specific sequence of intron 3 and a reverse primer that hybridizes to intron 4, such as a primer disclosed by Scheltinga or Yang, in order to have provided amplified fragments of exon 4 that could be sequenced and used to further define the HLA-A type. In the absence of unexpected results, reverse primers for amplifying exon 4 which hybridize to a locus specific region that terminates at position 501 of intron 3 or which consist of the sequence of SEQ ID NO: 205 would have been obvious in view of the teachings of Yang of the alignment of intron 3 HLA-A, HLA-B and HLA-C sequences, which alignment identifies the sequences at position 501 and 5' sequences surrounding position 501 as being conserved amongst HLA-A types and in view of the guidance of Yang for selecting additional locus-specific primers within intron 3. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers in a kit for the convenience of practioners in the art wishing to amplify and characterize exon 4 sequences.

Response to arguments:

In the response filed September 17, 2003, Applicants traversed the previous ground of rejection by stating that Yang does not teach amplifying exon 4. This argument is not convincing because Yang was not cited as teaching amplification of exon 4. Rather, Date and Scheltinga teach the amplification of exon 4. Applicants state that Yang only provided the motivation to amplify exon 2 and 3 together not separately. This argument is not convincing because as clearly state in the rejection and as clearly taught in the patent, Yang does in fact teach independently amplifying exon 2 and 3. Again, Yang

(column 5) states that "It will be appreciated, however, that exons 2 and 3 could be amplified individually by selecting a second amplification primer for exon 2 and a first primer for exon 3 which hybridize with intron 2 (SEQ ID Nos: 2, 5, and 8) ." Applicants reiterate their comments regarding their position that the cited art does not provide any guidance for selecting locus-specific primers. These arguments were addressed above and apply equally herein. Applicants state that the Scheltinga teaches only a sequencing primer. However, Schletinga and Date were cited as teaching the amplification of exon 4. Yang teaches intron 3 and teaches generating primers for the amplification of exons using sequences of the intron region. Further, Scheltinga also teaches that a polymorphism was identified in exon 4 which is useful in distinguishing between HLA-A types. Additionally, Date teaches amplifying exon 4 using a reverse primer that hybridizes to exon 4 and teaches that sequences within exon 4 can be used to distinguish different HLA-A types from one another (see pages 98-99). Accordingly, the prior art when considered as a whole would have lead the ordinary artisan to a method for simultaneously and independently amplifying exons 2, 3 and 4 of the HLA-A gene using locus-specific primers that hybridize to sequences within introns 2 and 3.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. This phone number will be changed after January 13 to (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
December 10, 2003

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER